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(54) **A process for hydrolyzing substituted methylenediphosphonic acid esters.**

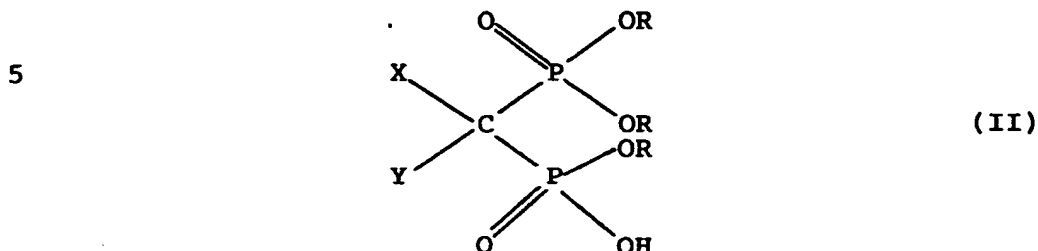
(57) **A process for hydrolyzing substituted methylenediphosphonic acid esters, by means of water only, to obtain highly pure acids, which may be directly used to prepare the corresponding salts, without isolating or purifying them.**

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A PROCESS FOR HYDROLYZING SUBSTITUTED METHYLENEDIPHOSPHONIC ACID ESTERS

The present invention relates to a process for hydrolyzing substituted methylenediphosphonic acid esters, of general formula II



10 wherein R is a C₁-C₄ straight or branched alkyl group, and X and Y, which may be the same or different, are hydrogen, an alkyl group or a halogen atom.

Processes for hydrolyzing esters of formula II, to obtain the corresponding methylenediphosphonic acids, and from these the corresponding salts, are known, for example, from U.S. Patent No. 3,213,030. Said processes use strong and concentrated acids at ebollition, for a long time. Particularly the ester of formula I, wherein R = i-propyl and X = Y = Cl, i.e. Cl₂C[PO(OC₃H₇i)₂]₂ is boil-
 20 ed with concentrated hydrochloric acid, to obtain dichloromethylenediphosphonic acid: Cl₂C[PO(OH)₂]₂. Said acid is then recovered by concentration of the reaction mixture, followed by two azeotropic distillations with isopropanol, to remove any traces of water and hydrochloric
 25 acid.

Said process presents some operative drawbacks,

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of boiling concentrated hydrochloric acid and to the subsequent azeotropic distillations.

In literature another process for obtaining the above dichloromethylenediphosphonic acid is known, consisting in pyrolyzing the corresponding tetraisopropyl ester. During this process, evolution of propene (gas) takes place, in a 4 moles/l mole of ester ratio, which constitutes a serious recovery and elimination problem, in industry.

10 The process of the present invention allows to hydrolyze the esters of formula II, using only water, at ebollition, during a certain time. The reaction, which takes place in complete absence of chlorides, allows to obtain the corresponding free diphosphonic acids in high
15 purity, which may be directly salified by means of alkali hydroxides in the aqueous solution from the hydrolysis, without isolating or purifying them.

 The hypothized hydrolysis mechanism is the following: the starting ester molecule, which is initially neutral, within a short time undergoes a partial hydrolysis, releasing a minimum amount of hydrogenions, sufficient to catalyze the hydrolysis. Said hypothesis is enhanced by the fact that, whilst usually the hydrolysis is complete within 10-12 hours, the hydrolysis time is shortened by
20 adding initially a small amount of the same methylenediphosphonic acid in solution, from a previous preparation.

 The process of the invention is therefore very simple, and provides remarkable advantages both by the economic and environmental points of view in the preparation of substituted methylenediphosphonic acids and salts
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economic and environmental points of view in the preparation of substituted methylenediphosphonic acids and salts thereof.

The process of the invention is described in more detail by the following non-limiting example.

EXAMPLE

Dichloromethylenediphosphonic acid disodium salt

a) Hydrolysis

250 Ml of deionized water and 50 g of pure tetra-
10 isopropyl dichloromethylenediphosphonate were placed in a three-neck flask, equipped with Vigreux column, distillation refrigerator and mechanic stirrer. The mixture was heated to ebollition (temperature of the head termometer: 80°C), keeping that temperature during all the hydrolysis
15 time.

The pH of the mixture was initially near neutral (between 6 and 7), after some minutes of ebollition, it fell to markedly acid values. The completion of the hydrolysis was checked by analytical measurement of the di-
20 chloromethylenediphosphonic acid content of the solution. The solution was decolorized by means of active charcoal, analyzed again to exactly measure its acid content, then directly used in the next step.

b) Salification

25 To the solution of step a), after cooling with ice-water, the stoichiometric amount of sodium hydroxyde in a 20% aqueous solution was added, to obtain the bisodium salt. The pH was adjusted to 4.2-4.5. The reaction mixture was cooled, treated with active charcoal, filter-
30 ed, warm concentrated till turbidity, then left to cry-

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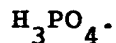
the product, which was combined with the first one. After drying, 41.5 g of the dichloromethylenediphosphonic acid bisodium tetrahydrate salt of formula $\text{Cl}_2\text{C}(\text{PO}_3\text{HNa})_2 \cdot 4\text{H}_2\text{O}$ were obtained. The purity of the compound was found to be 5 higher than 99%, and therefore suitable also for use in oral and parenteral pharmaceutical compositions.

<u>Elemental analysis:</u>	C	H	Cl	P
calc. % :	3.33	2.97	19.65	17.16
found % :	3.48	2.87	20.06	16.87.

10 Complexometric titre: 99.7%.

H_2O Content (K.F.) : calc.% 19.94; found % 20.2.

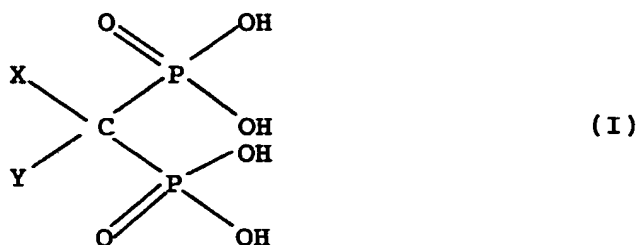
^{31}P -NMR Spectrum: sharp peak at -13.4 ppm referred to 85%



CLAIMS for the contracting states:

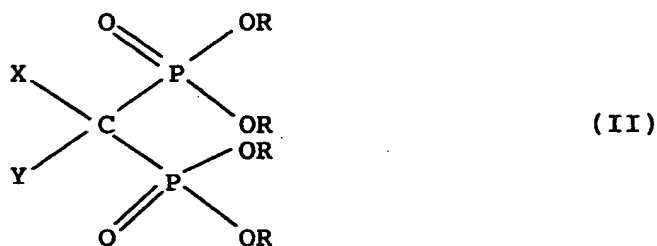
AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A process for preparing substituted methylenediphosphonic acids of general formula I



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wherein X and Y, which may be the same or different, are hydrogen, alkyl groups or halogen atoms, which process consists in hydrolyzing, using water only, the corresponding esters of general formula II



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wherein X and Y have the above mentioned meanings and R is a C₁-C₄ straight or branched alkyl group, optionally in the presence of catalytic amounts of an aqueous solution of the desired acid, from previous preparations.

2. A process as claimed in claim 1, wherein the hydrolysis is carried out at the boiling temperature of water.
3. A process as claimed in claims 1 and 2, wherein the

tetraalkyl ester of formula II is the isopropyl ester.

4. A process as claimed in claims 1 and 2, wherein the reagent is the dichloromethylenediphosphonic acid tetra-isopropyl ester.
- 5 5. A process as claimed in claims 1 and 2, wherein the reagent is the difluoromethylenediphosphonic acid tetra-isopropyl ester.



European Patent
Office

EUROPEAN SEARCH REPORT

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Application number

EP 86 10 5502

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ⁴)
Y	DE-A-2 745 982 (BAYER AG) * Page 4, last paragraph - page 5; page 20, examples 12,13; claims *	1-5	C 07 F 9/38
Y	DE-A-2 229 087 (BAYER AG) * Page 2, last paragraph - page 5, paragraph 1; claims *	1-5	
			TECHNICAL FIELDS SEARCHED (Int. Cl. ⁴)
			C 07 F 9/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 11-08-1986	Examiner BESLIER L.M.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	